REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments, the following remarks and the enclosed Rule 132 Declaration of the inventor herein Massimo FERRARI.

By this Amendment, claims 26, 28, 40, 44 and 45 have been amended. New claim 46 has been added. The amended claims and the newly added claim are all fully supported in the as-filed specification.

The claims presently pending in the application are 26-46, inclusive.

The rejections of claims 26-45, inclusive, under 35 U.S.C. § 112, second paragraph, are deemed to have been overcome by virtue of the amendments made herein.

In claim 40, the term "possibly" has been deleted.

In claim 28, the word "or" has been deleted between "presence" and "tributylamine" and --of-- has been inserted therebetween.

The original structure of Formula (VI) in claim 26 has been struck-through in its entirety.

In view of the foregoing, withdrawal of the § 112, second paragraph, rejection is respectfully solicited.

Claims 26-45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jones et al. U.S. 4,358,593 in view of Jones et al. EP 62503 and further in view of Alt, U.S. 5,523,416. This rejection is respectfully traversed.

The Examiner still maintains that the invention as recited in claim 26 is considered to be obvious under 35 U.S.C. § 103(a) over JONES 1 and JONES 2 and further in view of Alt, mainly on the following grounds.

(i) Jones 1 teaches in Example 14 the deprotection of acetoxy compounds of formula (VI)(with the treatment of sodium hydroxide in methanol followed by acidification to pH 2-3, which is in alignment with the claimed invention, then readjusted to pH 8 which results in the non salt raloxifene (I) (see Example 14 column 14).

(ii) Jones 1 does not teach the raloxifene HCl salt (I) as the final product, however Jones 2 teaches the deprotection can take place readily with sodium hydroxide in an alcoholic solution followed by acid catalysts (see col. 7, lines 17-68 and col. 8, lines 1-37.) It follows that the claimed invention reads on Jones 1.

Examiner's ground (i)

Jones 1 does not disclose the deprotection of acetoxy compound of formula (VI), but, on the contrary, discloses the homologue substituted with the pyrrolidine group. The sole example relating to the compound of formula (VI) is Example 26, which in any case discloses almost the same operating conditions as Example 14. In fact in both examples the alkaline deprotection is followed by the acidification (in example 14 the type of acid used in not mentioned, whereas in example 26 this acid is methanesulphonic acid and **not** hydrochloric acid). The acid treatment in both examples does not allow one to obtain the final salt, **but it is only an intermediate working condition**, before arriving **at the unsalified isolated product**, which in the case of example 26 is raloxifene.

Moreover, the operative conditions disclosed in these Examples, and specifically in Example 26, namely the alkaline hydrolysis followed by acid treatment with methane sulphonic acid, do not allow for high purity raloxifene to be obtained since, as indicated by example 26 of Jones 1, after the above treatment the **reaction product must be rendered basic once again with ammonia,** and **passed through a chromatographic column**. This type of treatment only allows a **yellow foam to be obtained;** to arrive at a product in crystalline form, a further treatment with acetone is required, to the ultimate detriment of the reaction yields.

The above considerations are also confirmed by the attached Rule 132 Declaration signed by Massimo Ferrari, one of the inventors of the instant Application in which the experiment of Example 26 is repeated.

The Declaration confirms that after the alkaline hydrolysis, the acidification to pH 2-3 with methane sulphonic acid results in the formation of a **small quantity of a gummy precipitate** (and **not,** as in the present invention with large quantities of a crystalline raw product, with a HPLC purity of 98%), as reported in Example 2B of the instant specification.

Moreover, this treatment with acid must be followed by a treatment with 30% aqueous ammonia to obtain a raw crystalline precipitate which, in any case is **not** the desired product in salt form. Furthermore, the yield obtained with respect to the acetoxy compound is decidedly lower (52.7%), than the yield obtained with the final raw raloxifene .HCl salt (65-70%) obtained with the process of the claimed invention and calculated with respect to the same starting compound.

In any case, the raw raloxifene precipitate resulting from the ammonia treatment does not require a crystallisation to be purified, but **a more drastic operating condition, which is most decidedly to be avoided in an industrial process**, namely, the purification by elution through a chromatographic column, which moreover does not allow one to obtain a crystalline product, **but rather an oily product**, which must first be subjected to a crystallisation, to become crystalline.!!!.

It is on this **isolated** product and **not** on the reaction mixture that Jones (1) suggests to carry out the salification with HCl according to the modalities reported at col.8, lines 27-29, namely, the isolated product, not the salified product, which must be dissolved in a suitable solvent through which HCl is bubbled.

In view of the foregoing, Jones 1 discloses, therefore, operative conditions which are decidedly far removed and decidedly misleading from those of the process claimed herein, wherein the **reaction mixture** and **not** the **isolated** crystalline product coming

from the alkaline hydrolysis with sodium hydroxide is **directly** treated with 37%HCl, namely, an aqueous solution containing large quantities of HCl.

Examiner's ground (ii)

Applicants respectfully traverse that the passage of Jones 1 at col. 7, lines 17-68 and col. 8, lines 8-37 addresses the process encompassing an alkaline hydrolysis followed by an acid treatment as in the process of the claimed invention.

Indeed, the passage at col. 7, lines 17-68 only states that the hydrolysis of the acetyl group may be **indifferently** carried out **both in an acid and a basic environment**. By contrast, the hydrolysis of the acetyl group in the presently claimed process is conducted **only** in a basic environment.

Although it is stated at col. 8, lines 8-37 of Jones 1 that the salts are quickly formed in high yields at moderate temperature and are obtained by suitably isolating the product from an acidic wash as the final step of the synthesis, Jones 1, in the same part, clearly teaches and directs one of ordinary skill in the art toward the preparation of hydrochloride salts by dissolving **the already isolated** raloxifene, in which hydrogen chloride is bubbled.

It follows from the above that one of ordinary skill in the art, from the combination of passages in Jones 1 which clearly teach:

- the hydrolysis of the acetyl group may be easily carried out **either in an acid environment, or in a basic environment,**
- to carry out the salification reaction with HCl on an **already isolated** raloxifene which is dissolved in a solvent in which HCl was bubbled,

would **not** have been motivated to think or believe that with the process of the invention, in which the acetyl group is removed in an alkaline environment and raloxifene .HC **is directly obtained** by adding a concentrated aqueous solution of HCl **to**

the reaction mixture, it would be possible to obtain a crude raloxifene .HCl salt in a solid form with a degree of purity **of about 98%** and also in high yield.

The teachings of Jones 2 and Alt do not serve to ameliorate the deficiencies in the teaching of Jones 1.

In view of the foregoing, the claims are deemed to distinguish over the combination of references employed by the Examiner in fashioning the rejection under 35 U.S.C. § 103(a). Accordingly, since the rejection has been overcome, its withdrawal is respectfully solicited and the issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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